Vitamin C deficiency in dialysis patients—are we perceiving the tip of an iceberg?

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Summary of the problem

The occurrence of vitamin C deficiency has complicated the management of dialysis patients since the beginning of renal replacement therapy [1]. The major portion of dietary vitamin C is provided by potassium-rich foods such as orange juice, strawberries and broccoli, but these foods are restricted for haemodialysis (HD) patients because HD removes potassium...
with limited efficiency. Hyperkalaemia is potentially a major risk factor for dialysis morbidity and mortality [2], and one of the chief responsibilities of the renal dietitian is to instruct the patient to limit the intake of potassium-rich foods [3]. Under these circumstances, low dietary vitamin C intake can readily occur. Since vitamin C is partly metabolized to oxalate, which can accumulate in renal failure patients, many clinicians only recommend a dose of 60–100 mg/day, which may not be optimal. The problem is made more severe by vitamin C losses during dialysis, which may remove several hundred mg of vitamin C in a single dialysis treatment [4,5]. Plasma vitamin C in dialysis patients is frequently <10 μM [6], a level associated with scurvy in the non-dialysis population. Normal plasma vitamin C levels in the non-dialysis population are 30–60 μM [7].

Very high levels of vitamin C can also occur in dialysis patients. The normal kidney clears vitamin C when the plasma level exceeds 60 μM [8], but the effect of dialysis on vitamin C is highly variable. For patients who take large vitamin C supplements, the lack of the normal renal clearance mechanism can result in very high plasma levels (>200 μM) [9].

Vitamin C deficiency can interfere with iron absorption and utilization, as well as leading to various abnormalities that are part of the syndrome of scurvy. The occurrence of widespread vitamin C deficiency in dialysis patients calls for greater attention to these clinical problems.

### Vitamin C and erythropoiesis

The biochemistry of vitamin C and iron are intimately related, and this has important repercussions in dialysis patients, for whom the bioavailability of iron for RBC production is a major concern.

At the level of the gastrointestinal tract, vitamin C helps maintain iron as Fe²⁺, which is more soluble than Fe³⁺ at the alkaline pH of the small intestine, and is more readily absorbed across the intestinal mucosa [10,11]. However, the iron requirements of dialysis patients are greater than most persons with normal renal function, and several investigations [12,13] have reported that oral iron supplements have limited ability to meet the iron needs of these patients. The consensus among dialysis clinicians is therefore that intravenously administered iron complexes (IV-iron) are obligatory in these patients, although further study may document beneficial effects of dietary vitamin C on utilization of oral iron.

Vitamin C can affect mobilization of iron from Kupffer cells and other sites in the reticuloendothelial system (RES). When storage iron accumulates beyond the requirement of the body for iron, it may be converted from ferritin to haemosiderin, a form of iron with limited bioavailability, which can accumulate in the bone marrow of dialysis patients [14]. Studies in guinea pigs have shown that vitamin C aids the conversion of haemosiderin iron to ferritin iron [15], which can be exported from the storage cell and carried on transferrin to sites of RBC synthesis in the bone marrow. In Bantu siderosis [16], administration of dietary vitamin C supplements led to a significant increase in serum iron, indicating that vitamin C was helping to mobilize stored iron in these patients. During the initial phase of vitamin C therapy in siderotic subjects, there was accelerated release of urinary oxalic acid [17], consistent with conversion of vitamin C to dehydroascorbate by interaction with stored ferric iron, followed by catabolism of dehydroascorbate to oxalate. Dialysis patients may also accumulate excess iron stores in the GI-mucosa [18], which could lead to rapid breakdown of vitamin C provided by the diet, and limit the impact of supplemental vitamin C on plasma vitamin C levels.

The chemical reactions between vitamin C and iron are shown below:

\[
\text{Fe}^{3+} (\text{ferric}) \rightarrow \text{Fe}^{2+} (\text{ferrous})
\]

**Fe³⁺ (ferric)**

**Fe²⁺ (ferrous)**

**Ascorbate**

**Dehydroascorbate**

**Oxalate**

IV-iron may only be partially utilized for Hb synthesis in dialysis patients. A dose of 1 g of iron could theoretically produce 300 g of Hb, which should increase Hb to 15 g/dl, from a baseline value of 10 g/dl. But the usual outcome of a standard 1 g course of IV-iron administered to HD patients is to increase Hb to only 11 g/dl [12,19], which indicates that 20% of the iron was available for Hb production. In a 1-year study of chronic kidney disease patients (stage 3 renal failure), a 2.4 g IV-iron regimen administered over 1 year led to 10–20% of the predicted increment of Hb in the bloodstream [20]; the remainder may have gone into long-term storage in the RES, and accumulation of large deposits of hepatic iron has been documented in HD patients after prolonged IV-iron therapy [21].

The interactions of vitamin C with intravenous iron complexes provide *in vitro* evidence for potential positive actions of vitamin C supplements in HD patients. These iron complexes contain relatively little ‘free’ iron, about 1–5% [22], and there is probably limited immediate release of iron to the bloodstream after injection. The iron complexes are generally taken into the lysosomal apparatus within a few hours [23,24], and the iron is released following decomposition of the complex within the storage cell [25]. However, at mildly acidic pH (ca 4–5), which is the pH of the lysosomal vacuole [26], vitamin C can release large amounts of the iron content from the complexes, and as much as 60% of the iron can be solubilized in several hours (Handelman, in preparation). Improved vitamin C status could assist in utilizing IV-iron after its uptake into the lysosome.
These actions of vitamin C have been exploited in several longitudinal studies that used intravenous vitamin C to improve erythropoiesis and decrease erythropoietin (Epo) requirements in patients with low Hb levels [27–29]. These investigators selected patients who required high Epo doses and who had elevated ferritin levels, indicative of a state of Epo resistance. Intravenous vitamin C (1000–3000 mg/week) was able, in many of these patients, to reduce Epo requirements and increase blood Hb levels, although negative results have also been reported [30]. Similar effects of high plasma vitamin C were observed in a cross-sectional study of plasma vitamin C and Epo requirements [31].

Vitamin C deficiency and scurvy in dialysis patients

Since dialysis patients can have plasma vitamin C <10 μM, the occurrence of scurvy is a possible outcome. Dialysis patients often have gingivitis, with additional diagnosis of periodontal disease [32], but vitamin C deficiency should be considered, since bleeding gums are a major scorbutic symptom. Dialysis patients frequently complain of fatigue; since fatigue is an early symptom of scurvy [33], the role of vitamin C deficiency should be explored further [34]. Scurvy is also associated with increased bone resorption [35] and impaired resistance to infection. Many of the symptoms of scurvy are seen in dialysis patients, and therefore specific diagnosis has been difficult to achieve. To resolve this controversy, a controlled-trial of vitamin C supplements in patients with low plasma vitamin C levels is warranted to examine its effect on scurvy-like symptoms.

Vitamin C and oxalosis

Systemic oxalosis was a complication of end-stage renal disease prior to the advent of reliable high-flux dialysis therapy. The manifestations included deposits of oxalate crystals in retina, skin, joints and cardiac muscle [36,37], and may in a few instances have been exacerbated by high-dose dietary vitamin C intake [38]. Following implementation of three times/week dialysis therapy, with weekly standardized Kt/V > 2, oxalate deposits could not be detected in a thorough biochemical analysis of biopsy and autopsy material from HD patients [39], and no case reports of oxalate deposition have been reported in recent years in dialysis patients as a result of vitamin C supplement use. The reaction to these earlier reports of harmful oxalate deposition has led to grave reservations about the use of vitamin C therapy for Epo resistance and other complications of HD, although some practitioners are currently using doses of 1000–3000 mg/week of vitamin C [28,29]. Other authorities take pains to argue that this practice is not safe [40]. A systematic study of oxalate acid accumulation and toxicity following vitamin C supplementation may be needed before vitamin C therapy can attain widespread use in the treatment of dialysis patients.

Summary and conclusions

Dietary restriction, concerns about oxalosis, losses during dialysis and accelerated catabolism have created a situation where a large portion (10–25%) of dialysis patients have plasma vitamin C levels <10 μM, and some patients have plasma vitamin C <2 μM [6] (Handelman, in preparation).

Epidemiological data suggest that these low plasma vitamin C levels are associated with increased mortality [41]. Although a 60–100 mg daily vitamin C supplement is generally recommended, prescriptions are provided only to 10–70% of patients, depending on nationality [42]. Lack of compliance may lead to even lower levels of actual vitamin C usage. Standardized clinical methods for measuring plasma vitamin C are needed, since the instability of vitamin C leads to problems in laboratory analysis [43,44], and vitamin C is not routinely measured in dialysis practice. Concerns about oxalosis need to be vigorously addressed, but if vitamin C is demonstrated to be safe, its more active use could lead to reduction of iron burden, more efficient erythropoiesis and alleviation of some of the scorbutic symptoms seen in HD patients.

Conflict of interest statement. None declared.